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ADDENDUM FOR NITROSAMINES

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PREFACE

Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five years. These addenda represent an updated literature search current as of 1988, plus additional information from Agency files and Program Offices. The first draft of this addendum was prepared by Syracuse Research Corporation under contract no. 68-C8-0004.

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
LOAEL	Lowest-observed-adverse-effect level
NOAEL	No-observed-adverse-effect level
P	Octanol/water partition coefficient
ppm	Parts per million
RfD	Reference dose
RQ	Reportable quantity

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Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority Pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five jears. These addenda represent an updated literature search current as of 1988, plus additional information form Agency files and Program Offices. This addendum is to update the existing Ambient Water Quality Criteria Document for Nitrosamines.

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The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is derived by dividing a NOAEL or LOAEL for subchronic or chronic exposure by standard uncertainty factor(s) times an additional uncertainty factor:

$$RfD = \frac{\text{NOAEL or LOAEL}}{UF(s) \times UF}$$

The standard uncertainty factors are applied to reflect the various types of data used to estimate RfDs. An uncertainty factor of 10 is used to account for variations in human sensitivity when extrapolating from valid human studies involving long-term exposure of average, healthy subjects. An additional 10-fold factor is used for each of the following: to extrapolate from long-term animal studies to the case of humans, to extrapolate from subchronic animal studies to chronic exposure, and to extrapolate from a LOAEL to a NOAEL. An additional uncertainty factor of >0-10 may be applied to reflect professional assessment of the uncertainties of the study and data base not explicitly addressed by the standard uncertainty factors (i.e., completeness of the overall data base). The default value for the additional uncertainty factor is 1.

In assessing the carcinogenic potential of a chemical, the U.S. EPA classifies the chemical into one of the following groups according to the degree of evidence in epidemiological studies and animal studies: Group A - Human Carcinogen; Group B - Probable Human Carcinogen [limited evidence in humans with or without sufficient evidence in animals (Group B1) or inadequate evidence in humans with sufficient evidence in animals (Group B2)]; Group C - Possible Human Carcinogen (limited evidence of carcinogenicity in animals in the absence of human data); Group D - Not Classifiable as to

Human Carcinogenicity (inadequate or no evidence); Group E - Evidence of Noncarcinogenicity for Humans. Quantitative carcinogenic risk assessments are performed for chemicals in Groups A and B, and on a case-by-case basis for chemicals in Group C. Upper-bound cancer unit risks (slope values) are estimated through the use of mathematical extrapolation models. Most commonly for animal data, the linearized multistage model with a 95% upper confidence limit is used to provide a low-dose estimate of cancer risk. The cancer risk is characterized as an upper-limit estimate (i.e., the true risk to humans, while not identifiable, is not likely to exceed the upper-limit estimate and in fact may be lower). Alternative risk models to the multistage model, such as the one-hit, Weibull, Logit or Probit model, are available and may be used when the evidence indicates that they may be more appropriate. In the absence of such evidence, the Agency recommends the linearized multistage model to provide consistency of approach and an upper-bound on the potential carcinogenic risk. In the case where human data are used for quantitative risk assessment, an upper-bound estimate rather than a 95% upper-bound estimate is used when low-dose linearity is assumed.

In the development of this Addendum to the AWQCD on nitrosamines, recent Agency assessments have been consulted. A computerized literature search was conducted to cover studies published more recently than the latest Agency assessment (i.e., published in 1986 to 1988). New key studies have been evaluated.

REVIEW OF NEW DATA

Toxicologic/Carcinogenic Effects

The U.S. EPA (1980) AWQCD addressed the class of organic compounds known as nitrosamines, many of which have been demonstrated to be animal carcinogens. Data were sufficient to derive cancer-based ambient water quality criteria for N-nitrosodimethylamine, N-nitrosodiethylamine, N-nitrosodi-n-butylamine, N-nitrosopyrrolidine and N-nitrosodiphenylamine. U.S. EPA (1980) recommended that the criteria for N-nitrosodiethylamine be adopted for the class and for members of the class for which data were not sufficient to confirm that cancer potency was less than that for N-nitrosodiphenylamine.

U.S. EPA (1980) also discussed nitrosamides as a related class and indicated that several of these compounds may also be carcinogens; however, the document did not review the literature on these compounds, and criteria were derived only for the nitrosamines. More recent evaluation of N-nitroso-N-methylurea and N-nitroso-N-ethylurea have resulted in the classification as U.S. EPA Group B2 (probable human carcinogens); however, no quantitative oral cancer potency estimates are available (U.S. EPA, 1987a,b).

Oral cancer potency estimates are available for the five nitrosamines for which U.S. EPA (1980) derived ambient water quality criteria, as well as for three members of the class not addressed by U.S. EPA (1980). In this section, for each of these chemicals the basis of the U.S. EPA (1980) water quality criteria derivation will be briefly presented followed by a discussion of the data that serve as the basis of the currently verified cancer potency estimate. This discussion will be followed by a review and evaluation of data not previously considered or more recent data that might have an impact on cancer risk estimation.

N-Nitrosodimethylamine

U.S. EPA (1980) ambient water quality criteria for N-nitrosodimethylamine are based on results of a study by Druckrey et al. (1967). As part of a carcinogenicity survey of 65 N-nitroso compounds, 4 mg N-nitrosodimethylamine/kg/day was administered in drinking water to 20 BD rats of unspecified sex for life. After an average induction time of 270 days, hepatocellular carcinomas developed in 11/20 rats. The average total dose to induce tumors in 50% of the rats was 0.4 g/kg and an inverse relationship was observed between dose and time to tumor. Control data were not reported.

Peto et al. (1984) conducted an extensive study using groups of 48 Colworth rats/sex, exposing them to doses of 0.033, 0.066, 0.132, 0.264, 0.528, 1.056, 1.584, 2.112, 2.640, 3.168, 4.224, 5.280, 6.336, 8.448 or 16.896 ppm N-nitrosodimethylamine in drinking water for life (with an additional 6 rats/group that were sacrificed after 6 and 12 months of treatment). Daily water consumption was ~41 and 72 mL/kg in adult males and females, respectively. Untreated control groups of 192 rats/sex were maintained, with 24 rats/group sacrificed after 6 and 12 months. Details of pathological methods were not reported. Liver tumors were subdivided histologically as to subsite of origin (i.e., adenomas or carcinomas); all other tumors were reported as benign or malignant. Female rats were slightly more sensitive to liver tumor formation than were male rats. Among the seven lowest dose groups, survival was good (median, 31 and 28 months of treatment, males and females, respectively). However, even at the lowest dose levels (0.033, 0.066 and 0.132 ppm), there was a positive trend in the proportion of animals with liver cancers. Direct evidence of carcinogenicity for the rat liver tumor was reported at a dose of ~0.1 ppm

(<0.01 mg/kg/day). Animals exposed to higher doses (≥2.112 ppm) experienced tumor-related mortality at ≤28 months. Pooled data from both sexes also showed possible positive trends for tumors in the lung, skin, seminal vesicles and lymphatic-hematopoietic system.

Lijinsky and Reuber (1984a) demonstrated that, when administered to F344 rats by gavage, N-nitrosodimethylamine (2 mg given twice a week) induced a high incidence of mesenchymal tumors of the kidney and alveolar-bronchiolar tumors as well as liver tumors. This is in contrast to administration of similar doses through drinking water, which results only in liver tumors.

Other recent data confirm that N-nitrosodimethylamine is a potent carcinogen in the strain A mouse pulmonary tumor assay (Anderson et al., 1982, 1986) and a liver carcinogen in hamsters (Lijinsky et al., 1987).

N-Nitrosomethylethylamine

U.S. EPA (1980) did not derive ambient water quality criteria for N-nitrosomethylethylamine, considering data on liver tumor formation in treated rats (Druckrey et al., 1967) to be insufficient for cancer potency estimation.

Druckrey et al. (1967) exposed groups of 4 and 11 BD rats to doses of 1 and 2 mg/kg/day N-nitrosomethylethylamine, respectively, for life via drinking water. Control rats were not included in this experiment, which was part of a survey of the carcinogenicity of 65 N-nitroso compounds. Hepatocellular carcinomas developed in a total of 9/15 animals. Average induction times and total doses to produce tumors in 50% of the rats were 500 days and 0.42 g/kg for the low-dose rats, and 360 days and 0.75 g/kg for high-dose rats. Esophageal tumors, the most prevalent tumor form associated with other asymmetrical nitrosamines containing a methyl group, were not found in rats treated with N-nitrosomethylethylamine.

Several shorter-term studies in F344 rats exposed to N-nitrosomethylethylamine in drinking water have been published. Male and female F344 rats receiving 3.0 mg N-nitrosomethylethylamine/day (8.6 mg/kg/day) in drinking water for 30 weeks showed a high incidence of hepatocellular carcinomas (19/20) as well as lung metastases and esophageal papillomas or carcinomas (Lijinsky and Reuber, 1981). Male rats receiving 600 or 3000 µg/week (0.24 or 1.22 mg/kg/day) in drinking water for 30 weeks also developed tumors: 3/20 hepatocellular carcinomas in the low-dose group and 12/20 hepatocellular carcinomas, nasal tumors, and esophageal papillomas in the high-dose group (Lijinsky and Reuber, 1980). Tumors of the liver (9/20) and nasal cavity (4/20) were also observed in male F344 rats receiving ~0.12 mg/day (~0.34 mg/kg/day) in drinking water over a 30-week period (Lijinsky et al., 1982). By contrast, female rats receiving drinking water containing 6 mg/L N-nitrosomethylethylamine (~0.84 mg/kg/day) developed leukemias (18/20 compared with 12/20 in controls). No other treatment-related neoplastic lesions were reported in females (Lijinsky et al., 1983). Michejda et al. (1984) reported that all of a group of 20 F344 rats administered 8 mg/kg/day N-nitrosomethylethylamine in drinking water for 15 weeks had died of liver tumors with a median time to death of 45 weeks.

N-Nitrosodiethylamine

U.S. EPA (1980) derived ambient water quality criteria for N-nitrosodiethylamine based on data from a study by Druckrey et al. (1963). In this study, groups of 25-80 BD-II rats were exposed via drinking water to doses ranging from 0.075-14.2 mg/kg/day N-nitrosodiethylamine, 7 days/week for life. All doses >0.15 mg/kg/day produced tumors in 100% of the surviving rats; these were predominantly in the liver (carcinoma, adenoma), with some

in the esophagus (carcinoma, papilloma). Lack of control data and the occurrence of intercurrent infections, especially among low-dose rats, complicated interpretation of these results.

Peto et al. (1984) treated 48 Colworth rats/sex/group throughout their lifetimes (starting at 6 weeks of age) with drinking water containing 15 concentrations of N-nitrosodiethylamine, ranging from 0.033-16.896 ppm. An additional 6 rats/group were treated for sacrifice at 6 and 12 months. Controls consisted of 192 rats/sex, 24 from each group sacrificed at 6 and 12 months with the remainder maintained until natural death. The extent of pathological examinations was not described, but tumors, except those of the liver, were classified either as benign or malignant only. Water consumption was 41 and 72 mL/kg for adult males and females, respectively. Survival was good at the seven lower doses, with median ages of natural death at 31 and 28 months for males and females, respectively. Tumor-related mortality in the higher dose groups occurred at $\leq$28 months. The predominant sites of tumor development were the liver and esophagus; mortality from all other causes of death combined was not significantly related to treatment. Data pooled by sex, however, showed possible positive trends for tumors of the lower jaw, nasopharynx, stomach, kidney, ovaries and seminal vesicles.

A corollary study was conducted by Peto et al. (1984) to determine the effect of age at the start of treatment or tumorigenesis by N-nitrosodiethylamine. Following the same protocol, rats were exposed starting at 3 or 20 weeks of age instead of 6 weeks of age as in the main experiment. Treatment commencing at the younger age resulted in a 3-fold higher incidence of liver tumors while a later start resulted in a 2-fold decrease. The effect on esophageal tumors was not large.

Peto et al. (1984) also administered the same range of doses of N-nitrosodiethylamine in drinking water to female Syrian hamsters and to female C57-B0 mice. A dose-related increased incidence of upper gastrointestinal and liver tumors was noted in the mice, and tracheal and liver tumors were reported in the hamsters.

Berger et al. (1987) exposed groups of 80 male Sprague-Dawley rats/group to 0.01, 0.032 or 0.1 mg/kg bw N-nitrosodiethylamine, 5 days/week via drinking water. Treatment started at 100 days of age and continued for life. A control group of 500 rats was maintained. A dose-related increased incidence in liver cancer was found (0.6, 2.5, 3.8 and 45% for control through high-dose groups, respectively). The increase in hepatic tumors was statistically significant ($p<0.05$) for all treatment groups. In addition, there was a 26% incidence of esophageal tumors in the high-dose (0.1 mg/kg) animals. These tumors were not observed at lower doses.

There is a large data base confirming the carcinogenicity of N-nitrosodiethylamine at multiple sites in several animal species, with much of this reported in the U.S. EPA (1980) document.

N-Nitrosodi-n-propylamine

U.S. EPA (1980) considered the available cancer data to be insufficient for derivation of ambient water quality criteria for N-nitrosodi-n-propylamine. As part of a survey of 65 N-nitroso compounds, Druckrey et al. (1967) provided BD rats (sex unspecified) with a diet that provided doses of 4, 8, 15 or 30 mg/kg/day N-nitrosodi-n-propylamine for life. Although the size of each treatment group was not reported, group sizes of 14, 16, 15 and 3 (from lowest to highest dose) can be inferred from the results of the study. Liver carcinomas developed in 45/48 test animals. The average tumor

induction times were dose-related ranging from 300 days (lowest dose) to 120 days (highest dose). At dose levels of 8 or 15 mg/kg/day, eight rats developed papillomas/carcinomas of the esophagus and six developed carcinomas of the tongue. Data on controls were not reported.

Numerous shorter-term studies of N-nitrosodi-n-propylamine have reported increased tumor incidences at several sites in two rodent and one monkey species exposed by various routes (Lijinsky and Taylor, 1978, 1979; Lijinsky and Reuber, 1981, 1983; Reznik et al., 1975; Pour et al., 1973; Althoff et al., 1973; Adamson and Sieber, 1979, 1983).

N-nitrosodi-n-propylamine administered to male Sprague-Dawley rats in drinking water at 1.8 mg/day (5.1 mg/kg/day) , 5 days/week for 30 weeks resulted in liver carcinomas (9/15), esophageal papillomas (6/15) and carcinomas (8/15) and nasal adenocarcinomas (8/15) (Lijinsky and Taylor, 1978, 1979). F344 rats of both sexes treated in a similar fashion with 0.9 mg/day (2.6 mg/kg/day) developed esophageal carcinomas (20/20) and forestomach tumors (12/20) (Lijinsky and Reuber, 1981).

Corn oil gavage of male and female F344 rats (2 times/week for 30 weeks) produced nasal and liver carcinomas, and esophageal tumors; tumors at these sites were not found in controls (Lijinsky and Reuber, 1983).

A high incidence of malignant tumors at distant sites, primarily nasal cavity, liver and lungs, was observed in Sprague-Dawley rats of both genders receiving lifetime weekly s.c. injections of 24.36, 48.72 or 97.44 mg/kg N-nitrosodi-n-propylamine (Reznik et al., 1975). Simillar studies in hamsters reported increases in tumors of the nasal cavities, laryngo-bronchial tract and lungs (Pour et al., 1973; Althoff et al., 1973).

Macaque monkeys given weekly i.p. injections of 40 mg N-nitrosodi-n-propylamine had a higher incidence of hepatocellular carcinomas (6/6) compared with that of presumed historical controls (7/90) (Adamson and Sieber, 1979, 1983). The average latency period was 28 months; the average total dose was 7.0 g.

N-Nitrosodi-n-butylamine

Ambient water quality criteria for N-nitrosodi-n-butylamine (U.S. EPA, 1980) are based on data from Bertram and Craig (1970) showing increased incidence of bladder and esophageal tumors in treated mice. Bertram and Craig (1970) administered the compound continuously for life via drinking water to groups of 50 C57Bl/6 mice/sex at concentrations of 60 or 240 mg/ℓ. Control groups were not maintained. Daily doses were calculated to be 7.6 and 8.2 mg/kg/day among low-dose males and females, respectively, and 29.1 and 30.9 mg/kg/day among high-dose males and females, respectively. Treatment was discontinued in about half of the high-dose animals after 197 days, when gross hematuria was noted in the majority of the high-dose males. Tumors, predominantly squamous cell carcinomas and papillomas in the esophagus and bladder, occurred in all treated mice. A total of 13 tumors of the soft palate and tongue were noted for all groups, and 5 tumors of the forestomach were found among low-dose animals. The hematuria noted during treatment occurred inconsistently and was believed to precede the appearance of bladder tumors.

BD rats of unspecified sex were fed diets that provided N-nitrosodi-n-butylamine at doses of 10, 20, 37.5 or 75 mg/kg/day, apparently for life (Druckrey et al., 1967). Inferred from the reported results, group sizes were 10, 10, 16 and 4, from lowest to highest dose. Based on the occurrence of liver carcinomas and malignant tumors of the

eosophagus and urinary bladder, average total dose to induce tumors in 50% of the rats in each group and the average time to induce tumors in 50% of the rats in each group were estimated at 3.9 g/kg and 540 days (10 mg/kg/day), 6.4 g/kg and 450 days (20 mg/kg/day), 8.3 g/kg and 262 days (37 mg/kg/day) and 10 g/kg and 150 days (75 mg/kg/day). When N-nitrosodi-n-butylamine was administered to rats by subcutaneous injection to circumvent the liver, only carcinomas of the urinary bladder resulted.

Several older inadequately designed experiments in various species using natural and parenteral routes of administration as well as a more recent 30-week gavage study in rats (Lijinsky and Reuber, 1983) were evaluated. Generally, these studies demonstrated high incidences of tumors in the liver, eosophagus, forestomach or bladder, depending on the species. Based on the abundant animal data, U.S. EPA (1986a) assigned N-nitrosodi-n-butylamine to U.S. EPA Group B2, a probable human carcinogen.

N-Nitrosopyrrolidine

Ambient water quality criteria for N-nitrosopyrrolidine (U.S. EPA, 1980) are based on carcinogenic effects in rats reported by Preussman et al. (1977). In this study, groups of equal numbers of male and female Sprague-Dawley rats (12-31/sex/group) were exposed to drinking water that provided N-nitrosopyrrolidine at doses of 0, 0.3, 1, 3 or 10 mg/kg/day for life. Increased mortality from pneumonia occurred in the highest dose group, believed by the authors to be due to a cumulative N-nitrosopyrrolidine respiratory toxicity. Dose-related increases in the incidence of hepatocellular carcinomas and adenomas were reported (statistically significant at $\geq$1 mg/kg/day), along with a concomitant decrease in latency period with increasing dose. The incidences of liver tumors were 0/61, 3/60, 17/62, 31/38 and 14/24 for the control through high-dose groups.

U.S. EPA (1986b) subsequently verified the cancer potency estimate for N-nitrosopyrrolidine derived by U.S. EPA (1980). In reviewing the available data, U.S. EPA (1986b) rejected from consideration earlier studies (complete references not provided) that associated liver and testicular tumors in rats and lung tumors in mice with orally-administered N-nitrosopyrrolidine.

Subsequent to the U.S. EPA (1986b) evaluation, Berger et al. (1987) administered N-nitrosopyrrolidine in drinking water that provided doses of 0.04, 0.133 or 0.4 mg/kg, 5 days/week for life to groups of 80 male Sprague-Dawley rats. A control group of 500 rats was maintained. The incidence of liver tumors was 3/500, 1/80, 4/80 and 17/80 in control, low-, middle- and high-dose groups, respectively (statistically significant, $p<0.002$, in the middle- and high-dose groups).

U.S. EPA (1986b) classified N-nitrosopyrrolidine in U.S. EPA Group B2, a probable human carcinogen, based on findings of tumors at more than one site resulting from oral administration of N-nitrosopyrrolidine to two rodent species and inadequate evidence in humans.

N-Nitrosodiethanolamine

Ambient water quality criteria for N-nitrosodiethanolamine have not been derived; insufficient data were available to U.S. EPA (1980) to assess human risk. Lijinsky and Kovatch (1985) exposed F344 rats starting at 7-8 weeks of age to drinking water 5 days/week at concentrations of 0, 28 or 64 mg/l for 100 weeks, with additional groups exposed to 64 or 160 mg/l for 50 weeks. The number of rats/sex/group ranged from 20-39. Histological examinations were conducted at natural death or when moribund, or at termination at 130 weeks. Survival was similar among treated and control groups until 100 weeks, but subsequent survival of treated males was shortened. A statistically significant ($p<0.001$) dose-related increase in

incidence of hepatocellular carcinomas and neoplastic nodules was seen in females exposed for 100 weeks (1/20, 10/39 and 14/20 at 0, 28 or 64 mg/ℓ, respectively). Corresponding incidences in males exposed for 100 weeks were 4/20, 6/39 and 11/20 at 0, 28 and 64 mg/ℓ, respectively. Statistical significance ($p<0.024$) was shown only for males exposed to 64 mg/ℓ and for females exposed to 64 mg/ℓ ($p<0.001$) and 28 mg/ℓ ($p<0.051$).

Preussmann et al. (1982) exposed groups of 36-38 male 100-day-old Sprague-Dawley rats to N-nitrosodiethanolamine (purity 99%) at doses of 0, 1.5, 6, 25, 100 or 400 mg/kg/day, 5 days/week for life via drinking water. At natural death or when moribund, histological examination of grossly abnormal organs or tissues from all rats was conducted. The incidence of total benign and malignant liver tumors was 0/88, 7/72, 43/72 and 33/36 in control and low-, middle- and high-dose groups, respectively. The incidence was significant at $\geq$6 mg/kg. Also, statistically significantly increased incidences of nasal cavity tumors (squamous cell carcinomas and neuroepitheliomas) were noted at doses of 100 and 400 mg/kg/day. Tumors at other sites were not considered to be treatment-related.

Higher-dose, shorter-term drinking water studies in rats (Lijinsky et al., 1980; Lijinsky and Reuber, 1984b), and a lifetime drinking water study with small groups of rats and no controls (Druckrey et al., 1967) associated exposure to N-nitrosodiethanolamine with liver tumors. Hamsters exhibited carcinomas of the nasal cavity and papillomas of the trachea from exposures by a variety of routes (subcutaneous, skin, oral swabbing) and for durations ranging from 27 weeks to lifetime (Hilfrich et al., 1978; Schmeltz et al., 1978; Pour and Wallcave, 1981; Hoffman et al., 1983).

N-Nitrosodiphenylamine

Current ambient water quality criteria for N-nitrosodiphenylamine (U.S. EPA, 1980) are based on carcinogenicity data from F344 rats (Cardy et al., 1979; NCI, 1979). In this experiment, N-nitrosodiphenylamine (98% pure) was administered at dietary concentrations of 0, 1000 or 4000 ppm (0, 50 or 200 mg/kg/day) for 100 weeks to groups of 50 6-week-old F344 rats/sex. Matched control groups of 20 rats/sex were maintained. Comprehensive pathological examinations were carried out on all moribund and dead animals and survivors, which were sacrificed at the end of the treatment period. Dose-related decreases in mean body weights were noted in all treated groups compared with controls. Mortality was dose-related among female ($p=0.024$) but not male rats. A significantly increased incidence ($p<0.001$) of transitional cell carcinoma of the urinary bladder occurred in high-dose groups of both sexes (16/45 for males, 40/49 for females); none occurred in control or low-dose rats. Dose-related increased incidences of fibromas of the integumentary system were noted in males, but these were not significantly higher than those in the controls.

NCI (1979) also exposed groups of 50, 6-week-old B6C3F1 male mice to diets containing 10,000 or 20,000 ppm N-nitrosodiphenylamine for 101 weeks, and used a similar protocol for females, except that dietary concentrations were adjusted during treatment, resulting in TWA concentrations of 2475 and 6139 ppm. Twenty matched controls/sex were also maintained. All treated mice had decreased body weight gain, but mortality was not significantly affected by exposure. Although there was a positive trend for transitional cell carcinoma in male rats, the incidence of this tumor in treated groups was not significantly different from controls. Treated mice of both sexes, however, showed submucosal inflammation and epithelial hyperplasia of the bladder.

In a more recent Agency analysis (U.S. EPA, 1987c) as well as in the literature search for the present effort, no additional positive cancer studies with N-nitrosodiphenylamine were located. U.S. EPA (1987c) classified N-nitrosodiphenylamine in U.S. EPA Group B2, probable human carcinogen, based on the increased incidence of bladder tumors in rats.

Bioconcentration Factor (BCF)

Presumably because data were insufficient for derivation of ambient water quality criteria, U.S. EPA (1980) did not estimate a weighted average BCF for N-nitrosomethylethylamine. The equation log BCF = (0.85 log P) - 0.70 (Veith et al., 1979) can be used to estimate the steady-state BCF for aquatic organisms that contain ~7.6% lipids (Veith, 1980) from the log P. A measured log P was not located in the available literature; therefore, a log P of 1.714 was estimated by using the method of U.S. EPA (1987d). Using the methodology described above, a steady-state BCF of 5.71 can be estimated for aquatic organisms containing 7.6% lipid. Correcting to 3% lipid content results in an average weighted BCF for N-nitrosomethylethylamine of 2.26.

Presumably because data were insufficient for derivation of ambient water quality criteria, U.S. EPA (1980) did not estimate a weighted average BCF for N-nitrosodi-n-propylamine. The equation log BCF = (0.85 log P) - 0.70 (Veith et al., 1979) can be used to estimate the steady-state BCF for aquatic organisms that contain ~7.6% lipids (Veith, 1980) from the log P. A measured log P of 1.36 was located (Hansch and Leo, 1985). Using the methodology described above, a steady-state BCF of 2.858 can be estimated for aquatic organisms containing 7.6% lipid. Correcting to 3% lipid content results in an average weighted BCF for N-nitrosodi-n-propylamine of 1.13.

Presumably because data were insufficient for derivation of ambient water quality criteria, U.S. EPA (1980) did not estimate a weighted average BCF for N-nitrosodiethanolamine. The equation log BCF = (0.85 log P) - 0.70

(Veith et al., 1979) can be used to estimate the steady-state BCF for aquatic organisms that contain ~7.6% lipids (Veith, 1980) from the P. A measured log P was not located in the available literature; therefore, a log P of -1.583 was estimated by using the method of U.S. EPA (1987d). Using the methodology described above, a steady-state BCF of 0.009 can be estimated for aquatic organisms containing 7.6% lipid. Correcting to 3% lipid content results in an average weighted BCF for N-nitrosomethylethylamine of 20.0036.

Pertinent new information regarding BCF values is currently undergoing Agency review for the remaining nitrosoamines; therefore, BCF values derived by U.S. EPA (1980) will be used in this document.

QUANTIFICATION OF EFFECTS

N-Nitrosodimethylamine

Current ambient water quality criteria for n-nitrosodimethylamine are 14.0, 1.4 and 0.14 ng/ℓ, corresponding to increased lifetime cancer risk levels of 10^{-5}, 10^{-6} and 10^{-7}, respectively (U.S. EPA, 1980). These values were calculated assuming a 70 kg body weight and a daily intake of 2 ℓ water and 6.5 g fish and shellfish with a BCF of 0.026 ℓ/kg. Criteria for ingestion of fish and shellfish alone are 160,000, 16,000 and 1600 ng/ℓ for the same respective increased cancer risk levels. These criteria were calculated from a potency factor of 25.88 $(mg/kg/day)^{-1}$, which was derived by applying a time-to-tumor model to the liver tumor data in the lifetime drinking water study in BD rats by Druckrey et al. (1967) (see Toxicologic/Carcinogenic Effects section).

More recently, U.S. EPA (1986c) derived a cancer potency factor for N-nitrosodimethylamine of 51 $(mg/kg/day)^{-1}$ from a study by Peto et al. (1984) in which rats, exposed via drinking water to a wide range of doses of N-nitrosodimethylamine for life, exhibited significant incidences of hepatocellular carcinomas (see Toxicologic/Carcinogenic Effects section). This potency factor was calculated using the Weibull model as this study was specifically designed for this type of analysis. Using the verified potency factor of 51 $(mg/kg/day)^{-1}$, and assuming 70 kg body weight and a daily intake of 2 ℓ of water and 6.5 g fish and shellfish with BCF for N-nitrosodimethylamine of 0.026, the criteria for N-nitrosodimethylamine in ambient water are as follows:

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (ng/ℓ)				
	0	10^{-7}	10^{-6}	10^{-5}	10^{-4}
2 ℓ of drinking water and consumption of 6.5 g of fish and shellfish	0	0.0686	0.686	6.86	68.6
Consumption of fish and shellfish only	0	812	8120	81,200	812,000

N-Nitrosomethylethylamine

Ambient water quality criteria were not derived by U.S. EPA (1980) presumably because the data were judged inadequate to assess risk. U.S. EPA (1987e), however, derived a potency factor of 21.75 $(mg/kg/day)^{-1}$ from the liver cancer data of the lifetime drinking water study in rats (Druckrey et al., 1967; Druckrey, 1967) described in the Toxicologic/Carcinogenic section. For this study, the one-hit model was deemed most appropriate for the derivation of the cancer potency factor. This potency factor was rounded to 22 $(mg/kg/day)^{-1}$ and verified, and is available on IRIS (U.S. EPA, 1987e). Criteria may now be derived based upon this verified value.

Using the unrounded verified potency factor of 21.75 $(mg/kg/day)^{-1}$, and assuming 70 kg body weight and a daily intake of 2 ℓ of water and 6.5 g fish and shellfish with a BCF for N-nitrosomethylethylamine of 2.26 (see Bioconcentration Factor section), the criteria for N-nitrosomethylethylamine in ambient water are as follows:

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (ng/ℓ)				
	0	10^{-7}	10^{-6}	10^{-5}	10^{-4}
2 ℓ of drinking water and consumption of 6.5 g of fish and shellfish	0	0.160	1.60	16.0	160
Consumption of fish and shellfish only	0	21.9	219	2190	21,900

N-Nitrosodiethylamine

U.S. EPA (1980) calculated ambient water quality criteria for N-nitrosodiethylamine to be 8, 0.8 and 0.08 ng/ℓ, corresponding to lifetime increased cancer risk levels of 10^{-5}, 10^{-6} and 10^{-7}, respectively, assuming a 70 kg body weight and a daily intake of 2 ℓ water and 6.5 g fish and shellfish with a BCF of 0.20. Criteria for consumption of fish and shellfish alone are 12,400, 1240 and 124 ng/ℓ for the same respective risk levels. These values were calculated from a cancer potency factor of 43.46 $(mg/kg/day)^{-1}$, which was derived by applying a time to tumor model to the liver tumor data in rats in the drinking water study by Druckrey et al. (1963) described in the Toxicologic/Carcinogenic Effects section.

More recently, the U.S. EPA (1986d) derived a potency factor of 150 $(mg/kg/day)^{-1}$ by applying the Weibull model to the data regarding liver tumors in female rats in the drinking water study by Peto et al. (1984) described in the Toxicologic/Carcinogenic Effects section. This value has been verified and is available on IRIS (U.S. EPA, 1986d). New criteria may appropriately be derived based on this new potency factor value.

Using the verified potency factor of 150 $(mg/kg/day)^{-1}$, and assuming 70 kg body weight and a daily intake of 2 ℓ of water and 6.5 g fish and shellfish with a BCF for N-nitrosodiethylamine of 0.20, the criteria for N-nitrosodiethylamine in ambient water are as follows:

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (ng/ℓ)				
	0	10^{-7}	10^{-6}	10^{-5}	10^{-4}
2 ℓ of drinking water water and consumption of 6.5 g of fish and shellfish	0	0.0233	0.233	2.33	23.3
Consumption of fish and shellfish only	0	35.9	359	3590	35,900

N-Nitrosodi-n-propylamine

U.S. EPA (1980) declined to derive ambient water quality criteria for N-nitrosodi-n-propylamine, judging that the available data were inadequate to allow risk estimation. U.S. EPA (1987f), however, applied the one-hit model to the liver tumor data in rats exposed for life to N-nitrosodi-n-propylamine in the lifetime drinking water study by Druckrey et al. (1967) described in the Toxicologic/Carcinogenic Effects section. The resultant potency factor of 7.02 $(mg/kg/day)^{-1}$, rounded to 7.0 $(mg/kg/day)^{-1}$, verified and available on IRIS (U.S. EPA, 1987f) is recommended as the basis for the new ambient water quality criteria.

Using the verified potency factor of 7.02 $(mg/kg/day)^{-1}$, and assuming 70 kg body weight and a daily intake of 2 ℓ of water and 6.5 g fish and shellfish with a BCF for N-nitrosodi-n-propylamine of 1.13, the criteria for N-nitrosodi-n-propylamine in ambient water are as follows:

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (ng/ℓ)				
	0	10^{-7}	10^{-6}	10^{-5}	10^{-4}
2 ℓ of drinking water and consumption of 6.5 g of fish and shellfish	0	0.497	4.97	49.7	497
Consumption of fish and shellfish only	0	136	1360	13,600	136,000

N-Nitrosodi-n-butylamine

The U.S. EPA (1980) derived ambient water quality criteria of 64, 6.4 and 0.64 ng/ℓ for N-nitrosodi-n-butylamine, corresponding to lifetime increased cancer risk levels of 10^{-5}, 10^{-6} and 10^{-7}, respectively. The values assume a 70 kg body weight, a daily intake of 2 ℓ water, and 6.5 g fish and shellfish per day with a BCF of 3.38. Criteria for intake of

fish and shellfish alone are 5868, 587 and 58.7 ng/ℓ, for the same corresponding risk levels. These values were calculated from a q_1^* (cancer potency factor) of 5.43 $(mg/kg/day)^{-1}$, which was derived by applying the linearized multistage model to data regarding the incidences of bladder and esophageal tumors in male C57Bl/6 mice in the dietary study reported by Bertram and Craig (1970) in the Toxicologic/Carcinogenic Effects section.

U.S. EPA (1986a) rounded the U.S. EPA (1980) q_1^* of 5.43 $(mg/kg/day)^{-1}$ to 5.4 $(mg/kg/day)^{-1}$, which is verified and available on IRIS. Using the unrounded potency factor of 5.43 $(mg/kg/day)^{-1}$, and assuming 70 kg body weight and daily intake of 2 ℓ of water and 6.5 g fish and shellfish with a BCF for N-nitrosodi-n-butylamine of 3.38, the criteria for N-nitroso- di-n-butylamine in ambient water are re-calculated as follows:

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (ng/ℓ)				
	0	10^{-7}	10^{-6}	10^{-5}	10^{-4}
2 ℓ of drinking water and consumption of 6.5 g of fish and shellfish	0	0.638	6.38	63.8	638
Consumption of fish and shellfish only	0	58.7	587	5870	58,700

N-Nitrosopyrrolidine

Ambient water quality criteria for N-nitrosopyrrolidine are 160, 16.0 and 1.60 ng/ℓ corresponding to lifetime increased cancer risk levels of 10^{-5}, 10^{-6} and 10^{-7}, respectively (U.S. EPA, 1980). These values assume a 70 kg body weight, and a daily intake of 2 ℓ water and 6.5 g fish and shellfish with a BCF of 0.055. Criteria for intake of fish and shellfish alone are 919,000, 91,900 and 9190 ng/ℓ for the corresponding risk

levels. The basis for these values is a q_1^* of 2.13 $(mg/kg/day)^{-1}$, derived by applying the linearized multistage model to the incidences of liver tumors in Sprague-Dawley rats administered this compound in drinking water for a lifetime in the Preussmann et al. (1977) study described in the Toxicologic/Carcinogenic Effects section.

The U.S. EPA (1986b) subsequently rounded and verified the U.S. EPA (1980) q_1^* for N-nitrosopyrrolidine of 2.1 $(mg/kg/day)^{-1}$. Using the unrounded verified q_1^* of 2.13 $(mg/kg/day)^{-1}$, and assuming 70 kg body weight and a daily intake of 2 ℓ of water and 6.5 g of fish and shellfish with a BCF for N-nitrosopyrrolidine of 0.055, the criteria for N-nitrosopyrrolidine in ambient water are re-calculated as follows:

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (µg/ℓ)				
	0	10^{-7}	10^{-6}	10^{-5}	10^{-4}
2 ℓ of drinking water and consumption of 6.5 g of fish and shellfish	0	0.00164	0.0164	0.164	1.64
Consumption of fish and shellfish only	0	9.19	91.9	919	9190

N-Nitrosodiethanolamine

Ambient water quality criteria have not been derived for N-nitrosodiethanolamine because data were inadequate (U.S. EPA, 1980). U.S. EPA (1987g) derived a q_1^* of 2.81 $(mg/kg/day)^{-1}$ by applying the linearized multistage model to the liver tumor incidence data in female rats from the 100-week drinking water study by Lijinsky and Kovatch (1985). U.S. EPA

(1987g) rounded the q_1^* of 2.81 $(mg/kg/day)^{-1}$ based on the Lijinsky and Kovatch (1985) study to 2.8 $(mg/kg/day)^{-1}$; this value is verified and available on IRIS.

Using the unrounded q_1^* of 2.81 $(mg/kg/day)^{-1}$, and assuming 70 kg body weight and a daily intake of 2 ℓ of water and 6.5 g fish and shellfish with a BCF for N-nitrosodiethanolamine of 0.0036, the criteria for N-nitrosodiethanolamine in ambient water are as follows:

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (μg/ℓ)				
	0	10^{-7}	10^{-6}	10^{-5}	10^{-4}
2 ℓ of drinking water and consumption of 6.5 g of fish and shellfish	0	0.00125	0.0125	0.125	1.25
Consumption of fish and shellfish only	0	106	1060	10,600	106,000

N-Nitrosodiphenylamine

Curent ambient water quality criteria for N-nitrosodiphenylamine are 49,000, 4900 and 490 ng/ℓ, corresponding to lifetime increased cancer risk levels of 10^{-5}, 10^{-6} and 10^{-7}, respectively (U.S. EPA, 1980). These values assume a 70 kg body weight, and a daily intake of 2 ℓ water and 6.5 g fish and shellfish with a BCF of 136 ℓ/kg. Criteria for intake of fish and shellfish alone are 161,000, 16,100 and 1610 ng/ℓ, corresponding to the same respective risk levels as above. These criteria are derived from a q_1^* of 4.92×10^{-3} $(mg/kg/day)^{-1}$ that was obtained by application of the linearized multistage model to the data regarding incidences of transitional-cell carcinomas of the urinary bladder in female F344 rats exposed to N-nitrosodiphenylamine in the diet (Cardy et al., 1979; NCI, 1979).

The U.S. EPA (1987h) has verified the rounded q_1^* of 4.9×10^{-3} $(mg/kg/day)^{-1}$ derived by U.S. EPA (1980) and used in formulation of current criteria. The verified value is available on IRIS and new criteria are not recommended at this time. Using the unrounded verified q_1^* of 4.92×10^{-3} $(mg/kg/day)^{-1}$, and assuming 70 kg body weight and a daily intake of 2 ℓ of water and 6.5 g of fish and shellfish with a BCF for N-nitrosodiphenylamine of 136, the criteria for N-nitrosodiphenylamine in ambient water are re-calculated as follows:

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (µg/ℓ)				
	0	10^{-7}	10^{-6}	10^{-5}	10^{-4}
2 ℓ of drinking water and consumption of 6.5 g of fish and shellfish	0	0.493	4.93	49.3	493
Consumption of fish and shellfish only	0	1.61	16.1	161.0	1610

Table 1 provides a summary of the criteria that have been derived for the eight nitrosamines discussed in this addendum.

TABLE 1

Summary of Criteria for Nitrosamines

Compound	Primary Site(s) of Cancer(s)	Species/ Strain	BCF	Cancer Potency Factor $(mg/kg/day)^{-1}$	Criteria For 10^{-6} Risk Level		Reference
					Water and Fish/Shellfish Consumption	Fish/Shellfish Consumption Only	
N-Nitrosodimethylamine	liver	Colworth rats	0.026	51	0.686 ng/ℓ	8120 ng/ℓ	Peto et al., 1984
N-Nitrosomethylethylamine	liver	BD rats	2.26	21.75	1.60 ng/ℓ	219 ng/ℓ	Druckrey et al., 1967
N-Nitrosodiethylamine	liver, esophagus	Colworth rats	0.20	150	0.233 ng/ℓ	359 ng/ℓ	Peto et al., 1984
N-Nitroso-di-n-propylamine	liver, esophagus, tongue	BD rats	1.13	7.02	4.97 ng/ℓ	1360 ng/ℓ	Druckrey et al., 1967
N-Nitroso-di-n-butylamine	esophagus, bladder	C57B1/6 mice	3.38	5.43	6.38 ng/ℓ	587 ng/ℓ	Bertram and Craig, 1970
N-Nitroso-pyrrolidine	liver	Sprague-Dawley rats	0.055	2.13	0.0164 µg/ℓ	91.9 µg/ℓ	Preussmann et al., 1977
N-Nitroso-diethanolamine	liver	F344 rats	0.0036	2.81	0.0125 µg/ℓ	1060 µg/ℓ	Lijinsky and Kovatch, 1985
N-Nitroso-diphenylamine	bladder	F344 rats	136	4.92×10^{-3}	4.93 µg/ℓ	16.1 µg/ℓ	Cardy et al., 1979; NCI, 1979

EXISTING STANDARDS AND CRITERIA

N-Nitrosodimethylamine

The verified oral and inhalation slope factor for N-nitrosodimethylamine is 51 $(mg/kg/day)^{-1}$ (U.S. EPA, 1986c).

ACGIH (1987) classified N-nitrosodimethylamine as an industrial substance that may be carcinogenic for humans, noting that exposure via skin can potentially contribute to overall exposure.

The proposed RQ for N-nitrosodimethylamine is 10 pounds (U.S. EPA, 1988a), based on potential carcinogenicity.

N-Nitrosomethylethylamine

The U.S. EPA (1987e) verified an oral slope factor for N-nitrosomethylethylamine of 22 $(mg/kg/day)^{-1}$.

N-Nitrosodiethylamine

The verified oral and inhalation slope factor for N-nitrosodiethylamine is 150 $(mg/kg/day)^{-1}$ (U.S. EPA, 1986d). The proposed RQ for N-nitrosodiethylamine is 1 pound (U.S. EPA, 1988b), based on potential carcinogenicity.

N-Nitrosodi-n-propylamine

The U.S. EPA (1987f) verified an oral slope factor for N-nitrosodi-n-propylamine of 7.0 $(mg/kg/day)^{-1}$.

N-Nitrosodi-n-butylamine

The verified oral and inhalation slope factor for N-nitrosodi-n-butylamine is 5.4 $(mg/kg/day)^{-1}$ (U.S. EPA, 1986a). The proposed RQ for N-nitrosodi-n-butylamine is 10 pounds (U.S. EPA, 1988c), based on potential carcinogenicity.

N-Nitrosodipyrrolidine

The verified oral and inhalation slope factor for N-nitrosopyrrolidine is 2.1 $(mg/kg/day)^{-1}$ (U.S. EPA, 1986b).

The proposed RQ for N-nitrosopyrrolidine is 1 pound (U.S. EPA, 1988d), based on potential carcinogenicity.

N-Nitrosodiethanolamine

The verified oral slope factor for N-nitrosodiethanolamine is 2.8 $(mg/kg/day)^{-1}$ (U.S. EPA, 1987g).

The proposed RQ for N-nitrosodiethanolamine is 1 pound (U.S. EPA, 1988e), based upon its potential carcinogenicity.

N-Nitrosodiphenylamine

The U.S. EPA (1987h) verified an oral slope factor for N-nitrosodiphenylamine of 4.9×10^{-3} $(mg/kg/day)^{-1}$.

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